APPENDIX

requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Some solvents that are known to cause unacceptable toxicities (Class 1, Table 1) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Some solvents associated with less severe toxicity (Class 2, Table 2) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, Table 3) should be used where practical. The complete list of solvents included in this guideline is given in Appendix 1.

The lists are not exhaustive and other solvents can be used and later added to the list. Recommended limits of Class 1 and 2 solvents or classification of solvents may change as new safety data become available. (The process for updating and maintaining the guideline is under review by the ICH Steering Committee.) Supporting safety data in a marketing application for a new drug product containing a new solvent may be based on concepts in this guideline or the concept of qualification of impurities as expressed in the guideline for drug substances (Q3A, Impurities in New Drug Substances) or drug product (Q3B, Impurities in New Drug Products) or all three guidelines.

2. Scope of the Guideline

Residual solvents in drug substances, excipients, or drug products are within the scope of this guideline. Therefore, testing should be performed for residual solvents when production or purification processes are known to result in the presence of such solvents. Although manufacturers may choose to test the drug product, a cumulative method may be used to calculate the residual solvent levels in the drug product from the levels in the ingredients used to produce the drug product. If the calculation results in a level below that recommended in this guideline, no testing of the drug product for residual solvents need be considered. If, however, the calculated level is above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent level to within the acceptable amount. The drug product should also be tested if a Class 1 or Class 2 solvent is used during its manufacture. If no Class 1 or Class 2 solvent is used in the manufacture or purification of the drug substance, excipient, or drug product, then a statement by the applicant or vendors to that effect would be acceptable and no testing would be necessary.

This guideline does not apply to potential new drug substances, excipients, or drug products used during the clinical research stages of development, nor does it apply to existing marketed drug products.

The guideline applies to all dosage forms and routes of administration. Higher levels of residual solvents may be acceptable for short-term (e.g., 30 days or less) or local application. Justification for these levels should be made on a case-by-case basis.

Given the implications of this guideline for the pharmaceutical industry and suppliers, a period of transition (approximately 2 years) will be provided when the guideline is finalized and implemented according to regional procedures (Step 5). See Appendix 2 for additional background information related to residual solvents.

3. General Principles

3.1 Classification of Residual Solvents by Risk Assessment

The term "tolerable daily intake" (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals, and the term "acceptable daily intake" (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The new term "permitted daily exposure" (PDE) is defined in the present guideline as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADI's of the same substance.

Residual solvents assessed in this guideline are listed in Appendix 1 by common names. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

(1) Class 1 solvents: Solvents to be avoided—

Known human carcinogens, strongly suspected human carcinogens, and environmental hazards.

(2) Class 2 solvents: Solvents to be limited—

Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity such as neurotoxicity or teratogenicity; solvents suspected of other significant but reversible toxicities.

(3) Class 3 solvents: Solvents with low toxic potential—

Solvents with low toxic potential to man; no health based exposure limit is needed. Class 3 solvents have PDE's of 50 milligrams (mg) or more per day.

3.2 Methods for Establishing Exposure Limits

See Appendix 3 for an explanation of the method used to establish exposure limits.

3.3 Options for Describing Limits of Class 2 Solvents

Two options are available when setting limits for Class 2 solvents.

Option 1: The concentration limits in parts per million (ppm) stated in Table 2 can be used. They were calculated using equation (1) below by assuming a product mass of 10 grams (g) administered daily.

$$(1) \qquad \text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}}$$

Here, the PDE is given in terms of mg/day and dose is given in g/day.

These limits are considered acceptable for all substances, excipients, or products whatever the dose and use. Therefore, this option may be applied if the daily dose is not known or fixed. Any excipient or drug substance that meets the limits given in Option 1 therefore may be used in any drug product. However, it is not considered necessary for each component of the drug product to comply with the limits given in Option 1.

Option 2: The PDE in terms of mg/day as stated in Table 2 can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in drug product. Such limits are considered acceptable provided that it has been demonstrated that the level has been reduced to the practical minimum, i.e., the limits are realistic in relation to the manufacturing capability and reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the use of Option 1 and Option 2 applied to acetonitrile in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus the Option 1 limit is 410 ppm. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and content of residual acetonitrile is given in the following table.

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	400 ppm	0.36 mg
Excipient 2	3.8 g	800 ppm	3.04 mg

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug product	5.0 g	728 ppm	3.64 mg

Excipient 1 meets the Option 1 limit, but the drug substance, excipient 2, and drug product do not meet the Option 1 limit. Nevertheless, the product meets the Option 2 limit of 4.1 mg per day and thus conforms to the recommendations in this guideline.

Consider another example using acetonitrile as residual solvent. The maximum administered daily mass of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and content of residual acetonitrile is given in the following table.

Component	Amount in formulation	Acetonitrile content	Daily exposure
Drug substance	0.3 g	800 ppm	0.24 mg
Excipient 1	0.9 g	2,000 ppm	1.80 mg
Excipient 2	3.8 g	800 ppm	3.04 mg
Drug product	5.0 g	1,016 ppm	5.08 mg

In this example, the product meets neither the Option 1 nor the Option 2 limit according to this summation. The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced during formulation to the allowed limit, then the manufacturer of the drug product should take steps to reduce the amount of acetontrile in the drug product. If all of these steps fail to reduce the level of residual solvent, in exceptional cases the manufacturer could provide a summary of efforts made to reduce the solvent level to meet the guideline value, and provide a risk-benefit analysis to support allowing the product with residual solvent at a higher level.

3.4 Analytical Procedures

Residual solvents are typically determined using chromatographic techniques such as gas chromatography. Any harmonized procedures for determining levels of residual solvents as described in the pharmacopoeias should be used, if feasible. Otherwise, manufacturers would be free to select the most appropriate validated analytical procedure for a particular application. If only Class 3 solvents are present, a nonspecific method such as loss on drying may be used.

Validation of methods for residual solvents should conform to ICH guidelines "Validation of Analytical Procedures: Definition and Terminology" and "Validation of Analytical Procedures: Methodology."

4. Limits of Residual Solvents

4.1 Solvents to Be Avoided

Solvents in Class 1 should not be employed in the manufacture of drug substances, excipients, and drug products because of their unacceptable toxicity or their deleterious environmental effect. However, if their use is unavoidable in order to produce a drug product with a significant therapeutic advance, then their levels should be restricted as shown in Table 1, unless otherwise justified. Toxicity data for Class 1 solvents are summarized in Appendix 4. The solvent 1,1,1,-Trichloroethane is included in Table 1 because it is an environmental hazard. The stated limit of 1500 ppm is based on a review of the safety data.

TABLE 1.—CLASS 1 SOLVENTS IN PHARMACEUTICAL PRODUCTS (SOLVENTS THAT SHOULD BE AVOIDED)

Solvent	Concentration Limit ppm	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1,500	Environmental hazard

4.2 Solvents to Be Limited

Solvents in Table 2 should be limited in pharmaceutical products. PDE's are given to the nearest 0.1 mg/day and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of determination. Precision should be determined as part of the validation of the method. Available toxicity data are summarized in Appendix 5.

TABLE 2.—CLASS 2 SOLVENTS IN PHARMACEUTICAL PRODUCTS

Solvent	PDE (mg/day)	Concentration Limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3,880
1,2-Dichloroethene	18.7	1,870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,N-Dimethylacetamide	10.9	1,090

TABLE 2.—CLASS 2 SOLVENTS IN PHARMACEUTICAL PRODUCTS—Continued

Solvent	PDE (mg/day)	Concentration Limit (ppm)
N,N-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethyleneglycol	3.1	310
Formamide	2.2	220
Hexane	2.9	290
Methanol	30.0	3,000
2-Methoxyethanol	0.5	50
Methylbutyl ketone	0.5	50
Methylcyclohexane	11.8	1,180
N-Methylpyrrolidone	48.4	4,840
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene[1]	21.7	2,170

[1] usually 60% m-xylene, 14% p-xylene, 9% o-xylene with 17% ethyl benzene.

4.3 Solvents with Low Toxic Potential

Solvents in Class 3 (shown in Table 3) may be regarded as less toxic and of lower risk to human health. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies. It is considered that amounts of these residual solvents of 50 mg per day or less (corresponding to 5000 ppm or 0.5 percent under Option 1) would be acceptable without justification. Higher amounts may also be acceptable provided they are realistic in relation to manufacturing capability and good manufacturing practice. Available toxicity data for Class 3 solvents are summarized in Appendix 6.

TABLE 3.—CLASS 3 SOLVENTS WHICH SHOULD BE LIMITED BY GMP OR OTHER QUALITY-BASED REQUIREMENTS

Acetic Acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl Acetate	Methylethyl ketone
tert-Butylmethyl ether	Methylisobutyl ketone
Cumene	2-Methyl-1-propanol
Dimethylsulfoxide	Pentane
Ethanol	1-Propanol
Ethyl acetate	1-Pentanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	Tetrahydrofuran

4.4 Additional Solvents

The following solvents (Table 4) may also be of interest to manufacturers of excipients, drug substances, or drug products. However, no adequate toxicological data on which to base a PDE were found. Manufacturers should supply justification for residual levels of these solvents in pharmaceutical products.

TABLE 4.—SOLVENTS FOR WHICH NO ADEQUATE TOXICOLOGICAL DATA WERE FOUND

1,1-Diethoxypropane	Methylisopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Petroleum ether
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

Glossary

Genotoxic carcinogens: Carcinogens that produce cancer by affecting genes or chromosomes.

LOAEL: Abbreviation for lowest-observed-adverse effect level.

LOEL: Abbreviation for lowest-observed effect level.

Lowest-observed-adverse effect level: The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity